Review Article

Imaging patients with TIAs

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Introduction

In the document entitled *The Health Of The Nation*, the British Government set the National Health Service a goal of reducing death from stroke by 40% by the year 2000.¹ This figure was derived from an extrapolation of the declining incidence of fatal stroke in England, as in most western countries,^{2,3} which has been attributed mainly to improvements in lifestyle, dietary habits, and treatment of hypertension and other risk factors. The Government indicated that it would give priority to those programmes targeted at the goals set by *The Health of the Nation*, as part of an overall strategy of achieving value for money. Therefore there is a strong financial incentive for hard-pressed hospital trusts to skim off some of this priority funding by setting up their own stroke services. However, unless this is done with care, there is every possibility that many will augment rather than diminish the incidence of disabling stroke in the communities they are serving.

In 1990 both the European⁴ and North American⁵ Symptomatic Carotid Endarterectomy Trialists (ECST and NASCET, respectively) reported their preliminary findings. These established carotid endarterectomy as a useful tool capable of conveying net benefit, thereby laying to rest many years of increasing uneasiness about its efficacy.⁶ However, so far benefit has been shown only for patients satisfying the following strict criteria: greater than 70% stenosis of the internal carotid artery ipsilateral to the symptomatic hemisphere, symptoms appropriate to that carotid supply territory, and other causes of stroke or stroke-like episodes absent. It also was shown that patients with less than 30% stenosis did not benefit from operation, despite the presence of symptoms appropriate for the supply territory of the diseased artery. Both groups of trialists cautioned strongly against unwarranted generalization of these results

to other types of stroke patients, or other patients believed to be at risk, such as those with asymptomatic carotid stenosis or vertebrobasilar disease.

The Oxfordshire Community Stroke Project has indicated that only 14% of patients with disabling or fatal stroke have a prior history of transient ischaemic attacks (TIAs)⁷ and it is recognized that only about 40% of patients with TIAs have major atheroma in the appropriate internal carotid artery.^{8,9} In both NASCET and ECST a pre-randomization condition was the presence of atheroma in the appropriate carotid artery of sufficient severity for a carotid endarterectomy to be considered on clinical grounds, and in ECST only one third had a stenosis of greater than 70%. Therefore the proportion of patients shown to benefit from operation constitutes no more than 2% of stroke patients in general, and since the number of strokes actually prevented could be in fact far less than this, the contribution of carotid endarterectomy towards achieving the goal set by *The Health of the Nation* seems small. Nevertheless this remains an important group to a stroke service and one which has major implications for imaging. Because of this, it is necessary to consider further aspects of these trials before focusing on imaging options.

The carotid endarterectomy trials

General features

Both trials contained approximately 750 patients. NASCET achieved almost equal numbers in the operated and non-operated groups but ECST had an excess of 135 patients in the operated group. Mean follow-up periods were 20 months in NASCET and 36 months in ECST. An event defining treatment failure was a stroke lasting longer than 24 hours in NASCET and longer than 7 days in ECST. NASCET assessed stenosis on prerandomization selective intra-arterial carotid arteriograms using a calibrated jeweller's eyepiece, and taking as denominator the diameter of the artery distal to the stenosis where it was judged to

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be normal; ECST was less specific about imaging modality and generally took as denominator the expected diameter of the carotid sinus. Therefore a stenosis in ECST would need to be about 20% greater to enter the greater than 70% stenosis group in NASCET. Finally, NASCET reported results from the severe stenosis group only, ECST for the severe and mild (less than 30% stenosis) groups. The results for both trials were similar but not by any means identical, and the more important differences are incompletely explained by the differences in method indicated above.

The results

The incidence of ipsilateral carotid territory stroke used to define treatment failure in the non-operated severe stenosis group was substantially higher during the follow-up periods than some workers had expected: NASCET 26.0%, ECST 13.6%. The incidence of disabling and fatal strokes which were defined similarly in both trials, was 13.1% in NASCET and 8.4% in ECST. In the operated groups, ECST showed that the incidence of ipsilateral carotid territory stroke fell to 1.9%, which was about the same as that in the unoperated mild stenosis group (1.3%); and in NASCET the incidence fell to 3.2%. Thus the trials showed that the increased risk of stroke associated with carotid stenosis could be eliminated by carotid endarterectomy.

About the results

The incidences of stroke in all groups in NASCET were about double those in ECST. This difference is not explained by the difference in definition of treatment failure, because it was observable also in subsets with disabling and fatal strokes where the definitions were similar. Although the severe stenosis group in ECST probably contained significant numbers of patients with less severe stenosis than in NASCET, the incidence of disabling and fatal stroke after carotid endarterectomy in NASCET also was about double that in ECST, so this is not an adequate explanation of the differences either.

A second important difference was the timing of the events defining treatment failure. In ECST virtually all the *excess* disabling or fatal strokes in the non-operated severe stenosis group occurred within 12 months of randomization and at least 85% within 9 months. Within a year, there was no significant difference between the incidence of stroke in the operated and non-operated groups, and in their report the trialists concluded that delay in surgery by just a few months may remove all its potential benefit. This was less apparent in NASCET, where the trialists were able to conclude

that carotid endarterectomy conveyed continuing benefit throughout the follow-up period. However, the data appeared to indicate that the benefit was tailing off by 18–20 months, and was less significant beyond this point, so it seemed possible that the NASCET trialists may revise their conclusion about continuing benefit as the mean follow-up period lengthens. At present it appears that the patients *actually* at risk of severe disablement or death from their severe carotid stenosis declare themselves within 2 years, and most do so far sooner, especially in Europe. This represents about 8% of the severe stenosis group in ECST and about 13% in NASCET. Although carotid endarterectomy removes 100% of the risk in these patients, they still represent only a small proportion of the symptomatic severe stenosis group, and only a tiny proportion of all patients subjected to prerandomization imaging.

This interpretation is in harmony with the results of studies in which patients were selected prior to carotid imaging, where it has been usual for no association to be found between the severity of carotid stenosis on angiography or sonography, and cerebral symptoms or computed tomographic (CT) evidence of cerebral infarction.^{9,10–13} It also is consistent with extensive autopsy data gathered about 30 years ago, in which brain slices had been evaluated together with the state of the cervical vessels,^{14,15} leading many workers to conclude that carotid stenosis *per se* is not a risk factor for stroke in most patients.^{9,16,17} Moreover, the evidence provided by therapeutic carotid ligation for various indications suggest that risk of disabling or fatal stroke from carotid occlusion is about 10–15%.¹⁸ In the carotid endarterectomy trials, the risk from severe carotid stenosis was so similar as to suggest that it is the effects of reduced perfusion pressure, rather than artery to artery atherothromboembolism, which is the main feature corrected by carotid endarterectomy.

Subset analysis in NASCET suggested that patients with less severe stenosis had less risk and that the gains from surgery were smaller than those in patients with more severe stenosis. Although this implies that within the severe stenosis group there may be a group at even higher risk, it of course is highly improbable that a linear relationship exists between severity of stenosis and stroke risk. Caution should be exercised before regarding an imaging modality which maximizes precision in estimating severity of stenosis, as essential to proper evaluation of stroke risk. Even in NASCET where stenosis was assessed by the most accurate form of carotid imaging available at the time, namely selective intra-arterial arteriography, inter-rater agreement on measurements made on the same films achieved a Kappa value of only 0.89. The many disagreements between the two observers

presumably arose due to difficulty in interpreting where the artery distal to the stenosis became normal, allowing for smallness due to reduced flow and the possibility of post-stenotic dilatation. Moreover, the precision of measurement on an individual film bears little relation to the accuracy with which the stenosis is depicted by the film. Most atheromatous stenoses are eccentric, and minor variations in projection angle can make a large difference to the apparent severity of the stenosis. This is the difficulty associated with using interval angiograms to study the natural history of atheromatous stenoses in general, and especially in a region as mobile as the neck where considerable variation in projection has to be expected.

The operative risk

The prevalence of stroke associated with carotid endarterectomy was 5.8% in NASCET and 7.5% in ECST. Most strokes occurred at the time of operation and about half resulted in permanent severe disability or death. The NASCET trialists⁵ concluded in their report that 'if the rate of major complications approaches 10%, the benefit [of carotid endarterectomy] will vanish altogether'. They also added that 'the benefit reported here should be adjusted downwards to include the risk of prerandomization arteriography'.

The risk of death or disablement associated with arteriography realistically is about 1–2%,^{19,20} and applies equally to both operated and non-operated patients. If a stroke service adopts the policy that all patients considered for carotid endarterectomy should have intra-arterial carotid arteriography, as was the case in NASCET, for example, all the benefit gained by operation would be wiped out if the stroke rate due to arteriography were to rise even minimally above 1%.⁵ The author also is concerned that the operative risks as defined above may underestimate the prevalence of brain damage associated with carotid endarterectomy. In our unit the prevalence of new brain infarcts detected by CT after operation has been about 8%, which represents most patients rescanned because of a postoperative neurological deficit, but the prevalence of perioperative disabling or fatal stroke in the same unit has been audited as only 1.6%. This is quite legitimate because the trial protocols exclude events depicted by brain imaging only and not accompanied by persisting clinical effects.

We are now in a position to consider the imaging options available to patients with TIAs, which also apply to those with non-disabling strokes and retinal infarction or ischaemia, all of whom have an increased risk of major stroke in the near future over patients of similar age without such symptoms.

The imaging options

Brain imaging

This should be the first type of imaging contemplated. Even in a unit as experienced as our own, the occasional brain tumour (usually a metastasis) is recognized as the actual cause of stroke-like episodes after a carotid endarterectomy has been performed. Transient or minor neurological deficits can result from intracranial haemorrhages, and sometimes also from surprisingly extensive infarctions. Brain infarction is not shown reliably by CT or magnetic resonance imaging (MRI) within the first 24 hours of onset of neurological dysfunction; most, if they are going to show at all, which is in about 80% of major clinical events, do so within 3 days of continuing dysfunction. Haematomas are clearly shown by CT as high density masses within about 2 hours of extravasation; haematomas less than 2 or 3 days old are shown by MRI, but the appearances are less specific than on CT in this early period. After 5–10 days, the appearance of a haematoma on MRI is at least as specific as on CT, and becomes progressively more so as time passes.

The prevalence of ischaemic brain damage revealed by CT and MRI in patients with TIAs is about 40% and 70%, respectively.^{11,21} Since most of the abnormalities shown are multifocal or diffuse, and often are confined to the clinically relatively ineloquent white matter or basal ganglia, their relevance to focal clinical events is uncertain. Nonetheless it is these abnormalities that show the clearest association with the most important risk factors for stroke in general, namely, increasing age, past history of stroke and hypertension.^{16,22–24} By contrast severe carotid stenosis is a far less frequent finding in these patients, showing only an association with increasing age, and not with past history of stroke or hypertension.¹⁷ The prevalence of this type of diffuse white matter disease has been appreciated only since computed brain imaging, because usually it was not apparent on routine inspection of brain slices at autopsy. These brain changes usually are linked closely with small vessel disease, most frequently arteriolar hyalinosis. The role of this process as a cause of symptomatic cerebrovascular disease often is ignored and undoubtedly has been underestimated.

The distribution of focal brain damage shown by CT or MRI gives some indication of its probable cause, but on occasions it can be misleading. Most large cortical infarcts and isolated infarcts involving deep structures are associated with normal cervical vessels, and are likely to be the result of large emboli usually arising in the heart.²⁵ Patients with watershed infarctions can be divided into two groups: those with normal cervical vessels who

probably have had embolic infarcts which happen to simulate a watershed pattern, and those with severe proximal arterial stenosis or occlusions who probably are suffering from the effects of reduced perfusion pressure. These latter patients usually have severe disease in multiple extracranial vessels, most frequently associated with one or more occlusions though not necessarily on the side of the infarction.¹¹ An association has been found between carotid stenoses that appear 'irregular' on arteriograms and small mainly juxtacortical ipsilateral infarcts on CT, which bear striking similarity to the small infarcts often shown in patients who have had a stroke during arteriography. Such cerebral lesions have been proposed as the usual appearance of artery to artery artherothromboembolism in the brain. Too much emphasis should not be placed on this, however, because interpretation of the images can be difficult and subjective, and these lesions provided evidence for artery to artery embolism in only 12% of symptomatic cases.¹¹

Vascular imaging

Studies in which cerebral angiography was performed within a few hours of onset of a major stroke have shown embolic arterial occlusions in 40–70% of cases.^{26,27} However, such studies usually have included a large proportion of young patients with acute stroke, who simply are not relevant to the great majority of older patients presenting with TIAs. For the latter vascular imaging is concerned mainly with excluding carotid stenosis. Although the indications for vascular imaging in stroke patients in general are wider than this, in practice the treatment options which could be influenced by other findings are limited, and on rare occasions when there is major diagnostic uncertainty, the uncertainty usually is not reduced by extensive angiography. Thus the most important part of the vascular tree to image is the carotid bifurcation ipsilateral to the symptomatic hemisphere. Just how necessary it is to know the state of the contralateral vessels and the vertebrobasilar system is conjectural, and various experts hold strong but discordant views. In the authors' opinion, the best approach for most patients is to use the safest technique and, when this involves risk, to do as little as possible. Many techniques are available, none of which are ideal.

X-ray imaging

This requires iodine-based contrast media, which may be injected into central veins and imaged in the cerebral arteries after traversing the pulmonary vascular bed, or they may be injected via a catheter directly into the aortic arch or selectively into

individual arteries. Computerized subtraction techniques are usually used to enhance contrast, and these forms of angiography generally are referred to as intravenous (i.v.) or intra-arterial (i.a.) digital subtraction angiography (DSA).

Intra-arterial DSA usually is regarded as the gold standard for imaging carotid disease and estimating percentage stenosis. Computer processing DSA has made possible the use of smaller volumes of contrast media, and modern angiography uses smaller catheters and iso-osmolar contrast media, but unfortunately these technical advances have not resulted in a significant reduction in risk of stroke during the examinations. Aortic arch injections appear just as dangerous as selective catheterization of the carotid arteries themselves.²⁰ This suggests that most angiographically induced strokes in carotid territory are caused by thrombi within the catheter system.

Intravenous DSA is safe. In the mid-1980s a series of papers appeared in North America which suggested it was not. This resulted in Hankey and Warlow¹⁹ concluding that major systemic complications (which included cardiac failure, myocardial infarction, arrhythmias, pulmonary oedema and death) occurred in 18% of examinations. As those who continue to use this technique know and as many large prospective studies have shown, this simply is not true. Intravenous DSA does not carry any risk of stroke and the risk of minor systemic complications is about 0.6%, the commonest being chest pain usually interpreted as angina.²⁰

An i.v. displays the entire vascular tree from aortic arch to intracranial vessels; it is rapid and requires little operator skill.

Intravenous DSA is less accurate than i.a. DSA, mainly because of the lower density of contrast medium in the arteries and the frequency of subtraction artefacts. Indeed about 50% of the examinations are suboptimal for one reason or another, although less than 10% are truly non-diagnostic, such that an i.a. DSA is essential for clarification. Nevertheless, this aspect has caused such concern that most units around the world have abandoned i.v. DSA and use only i.a. DSA when angiography is required, on the assumptions that accurate demonstration of stenosis is essential to estimation of stroke risk, and i.a. DSA provides this accuracy, both of which, as we have seen, are very likely to be incorrect. The arguments against the safety of i.v. DSA have provided vital support for this policy which, in the author's opinion, has encouraged their exaggeration. The fact remains that when i.v. DSA is used in combination with a non-invasive test such as sonography, its accuracy is enhanced sufficiently to almost eliminate the need for preoperative intra-arterial angiography. A unit pursuing such a policy optimizes the risk to benefit relationship for carotid endarterectomy.

Sonography

Sonographic imaging of the carotid bifurcation has improved markedly in recent years, due to advances in equipment design and performance.²⁸ Stenosis can be measured and plaques characterized as calcified, echogenic or echolucent. Adherent, thrombus and ulceration may not be identified more reliably than they are by contrast angiography. Using continuous wave Doppler, blood velocity can be estimated and related to percentage stenosis; direction of flow can be revealed by colour flow techniques. Carotid sonography is absolutely safe, but can be time consuming and requires highly trained personnel to be reliable. It generally provides information only about the carotid bifurcation. Accuracy usually is good but even in experienced hands major errors are made occasionally. These errors used to run at about 10%, of which 2–5% were very significant. Better equipment has improved this but it is still not perfect. A few vascular surgeons are satisfied with its accuracy and accept its limitations sufficiently to perform carotid endarterectomy on sonographic findings alone. Such a policy may optimize the risk to benefit relationship for carotid endarterectomy but significant doubt must remain about the appropriateness of some of the operations performed on this basis.

Many enthusiasts for sonography are placing increasing emphasis on plaque characterization. This is believed to indicate which plaques may be unstable, and therefore prone to intraplaque haemorrhage, ulceration and embolism. It is often claimed that the sonographic characteristics of plaques show an association with the prevalence of ipsilateral cerebral ischaemic symptoms, whereas percentage stenosis does not.^{9,12} Exactly which features characterize high-risk plaques have not yet been agreed by all workers.

Magnetic resonance angiography (MRA)

This technique does not require injection of contrast media and, therefore, like sonography, is completely safe. It is capable of showing the aortic arch and intracranial vessels, as well as the cervical arteries; it can also selectively show the cerebral veins and dural sinuses.²⁹

Normal vessels usually are shown well, including the middle cerebral artery and its major branches. Neck coils are used for imaging cervical vessels, which are then exchanged for head coils to image the intra-cranial vessels. Data acquisition times now are down to 6–10 minutes per region but processing times can be longer. Technical improvements are constantly being made at present, so the literature on efficacy is soon out of date. MRA images laminar flow better than turbulent

flow and is very sensitive to patient movement. Abnormal flow patterns due to stenosis can result in confusing or deceptive appearances; for example, a vessel with a tight stenosis may not be visible at all either above or below a stenosis, or a stenosis may appear longer than it actually is. In general percentage stenosis tends to be overestimated in abnormal cases and the abnormal contours due to irregular atheroma so familiar on conventional arteriography may not be reproduced on MRA.

The technology currently is available to measure flow velocity and direction, and to do so more accurately than sonography. There is also the potential of characterizing plaques in terms of their internal structure on magnetic resonance imaging, which may be more specific than is possible with sonography. Therefore MRA performs all the functions of sonography, and is far more versatile and not so dependent on the operator. The author anticipates MRA eventually replacing carotid sonography.

Other imaging

This is not an exhaustive review of the types of imaging that are possible. It is intended to be a guide to those most commonly considered at the present time. The various brain imaging methods that display blood flow and metabolism can be used, but in general they show so many non-specific abnormalities in this type of patient that their clinical role has long remained minimal.²⁹

Planned imaging of patients with TIAs

1. *Brain imaging* (CT or MRI) to detect haemorrhages and neoplasms, and to demonstrate the pattern of ischaemic brain damage which may provide a better guide to the most probable cause of symptoms than angiographic findings, or indeed clinical features.
2. *Clinical considerations* tuned to decide whether an individual patient has a reasonable chance of benefiting from carotid endarterectomy. This consists of a tailored estimate of the net benefit which may reasonably be expected when the risks of carotid endarterectomy are weighed against the possible benefit for that individual patient.
3. *Screening for carotid stenosis.* Use MRA or sonography. Sonography is now dominant but will probably be supplanted by MRA.
4. If a stenosis has been shown which is likely to be significant, use i.v. DSA. The entire vascular tree from aortic arch to intracranial circulation will be shown, providing an opportunity to

consider unusual therapeutic strategies for unusual cases.

5. If i.v. DSA is inadequate, use i.a. DSA to image the single vessel of interest only.

The majority of patients with TIAs should not proceed as far as step 4, and very few indeed should proceed to step 5. By the time patients are considered for step 5, it would seem most sensible for them to be transferred to a centralized unit with

recognized special expertise both in performing carotid endarterectomy and cerebral arteriography. This centre should be audited, and the results of audit made available to contracting agencies, because this will influence the decision involved in step 2, namely the appropriateness for an individual patient to be considered for carotid endarterectomy.

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